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EXAMINER	
AKHAVAN, RAMIN	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/713,006	DUPRET ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *17 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *Dec. 2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are pending and under consideration in this action.

Sequence Compliance

The specification discloses sequences (¶ 0062)[1] that are not properly identified with sequence identifiers (i.e., "SEQ ID NO:"). See 37 CFR 1.821-1.825 and MPEP §§ 2421-2431. The requirement for a sequence listing applies to all sequences disclosed in a given application, whether the sequences are claimed or not. See MPEP § 2421.02. If said sequences were originally submitted in both electronic and paper format, then applicant is only required to make proper amendment to the sequences (i.e., with proper sequence identifiers). However, if applicant has not previously submitted said sequences, then a new submission is also required (i.e. CD-ROM/CD-R, Paper Listing and Attorney Declaration).

Specification

The disclosure is objected to because of the following informalities. Regarding the description of the drawings for Figures 4-6, there appears to be discord between what is described and what figures are present in the corresponding figures. (Specification, ¶¶ 0042-44). In particular, the descriptions do not correlate to the figures as follows: the description for Fig. 4 is for a "preparation of ssDNA..." but Fig. 4 depicts a vector schematic; the description for Fig. 5 is for "ssDNA preparation..." but Fig. 5 depicts a gel digest photograph; and the description for Fig. 6 is for digestion results, but Fig. 6 depicts a schematic with subparts A-C.

[1] All references to the specification correspond to the published version of this application, i.e., US 2004/0214197.

In addition, the portion of the specification defining "at least two homologous heteroduplex polynucleotides" is unintelligible, as the definition comprises grammatical and typographical errors. (¶ 0021).

The specification further comprises multiple typographical/grammatical errors. The term "strain" is misplaced in describing SSB proteins. (¶ 0009). The terms "eukaiyotes" (¶ 0008), "enor-prone" (¶ 0049), "olitronucleotides" (¶ 0061) and the phrase "1 g[ram] of PCR product" contain typographical errors. The term "products" should be inserted after the term "PCR" and the number "5' " should replace "5" to maintain consistency with Fig. 5. (¶ 0075).

Further, under the section for "Fragmentation-Assays", additional typographical errors are present. (¶ 0084). The description recites the following terms/phrases: "assays were carried out in 20 1"; "5°mM"; "40 *g* bovine serum albumin" (emphasis added); and "30 1 of 25". Appropriate correction of the foregoing errors is required.

Claim Objections

Claim 14 is objected to because it contains a typographical error, i.e., the term "conibination".

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

1. **Claims 1-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.**

Claim 1 (and dependent claims) recites the limitation "said heteroduplex" but it is unclear to which heteroduplex said limitation is directed (i.e., base claim delimits two distinct heteroduplex molecules).

In addition, as written claim 1 is directed to action steps, components or elements, which do not interrelate. More particularly, the claim encompasses exposure of at least a single heteroduplex to a repair system so as to produce at least one annealed fragment. The claim is indefinite because the heteroduplex, by definition, already comprises annealed strands (or a fragment) and the duplex is certainly a polynucleotide fragment. In other words, the beginning substrate, i.e., the duplex, *is* an annealed fragment comprising two polynucleotide strands. Thus, it is unclear what is being claimed.

Furthermore, claim 1 recites the phrase "one homologous heteroduplex polynucleotide", which confers ambiguity and is vague. The source for the ambiguity is that the specification defines the term "homologous" and "heteroduplex" to mean substantially the same thing and the only definition for said phrase defines not "one" but "two homologous heteroduplex polynucleotides". More particularly, the term "homologous" is defined as "polynucleotides that differ from each other at least at one corresponding residue". (¶ 0019).

Similarly, the term "heteroduplex polynucleotides" is defined to mean double-stranded polynucleotides with imperfect complementation. (¶ 0020). Thus, two different limitations are defined to mean essentially the same thing. As such, it is unclear what metes and bounds define

the claimed method. Further, the phrase "one homologous heteroduplex" is not defined, but the phrase "two homologous heteroduplex polynucleotides" is indicated to mean the following as recited in the specification:

> The phrase at least two homologous heteroduplex polynucleotides refers to a plurality of double-stranded polynucleotides, wherein a strand of each double-stranded polynucleotide are [sic] not only *imperfectly complementary* to its opposed strand but also differa [sic] from the corresponding strand of one of the other double-stranded polynucleotides at least at one corresponding residue position. In other words, the heteroduplex polynucleotides are homologous to each other. (emphasis added) (Specification, ¶ 0021).

Thus, if the cited passage is extended to define the limitation "one homologous heteroduplex", then the limitation contains redundant terms as is discussed above (i.e., regarding the terms "homologous" and "heteroduplex", defined to mean imperfectly complementary, or not matching at least at one corresponding residue). In sum, it is unclear what method claim 1 is defining, because as written, the claim comprises limitations that are redundant thus vague and indefinite.

In addition, claim 1 recites the limitation "until", which limitation is vague and indefinite. In other words, one of skill cannot determine what amount of time satisfies the limitation "until". If broad coverage is sought, then the term should simply be omitted to obviate this ground of rejection (e.g., where exposure to a "repair system" results in at least one annealed fragment).

Claim 1 recites "said fragment" which does not find sufficient antecedent support. Further, it is unclear how "said fragment" is concomitantly an "annealed fragment" and a single stranded fragment, owing to the fact that the denaturing action step necessarily results in a single stranded molecule. The claim must be amended to better define the structure of "said fragment".

Claim 1 recites the phrase "obtaining said fragment", which does not interrelate to the preamble, where the preamble recites "preparing polynucleotide fragments". It would be remedial to replace the former phrase with "preparing said fragments".

In addition, regarding the step of exposing the heteroduplex to a repair system until the heteroduplex comprises "at least one annealed fragment", as written, it is unclear whether the step of "exposing" a heteroduplex results in an annealed fragment. As noted above, the heteroduplex already comprises one strand annealed to another strand, as would any heteroduplex. The specification does not further clarify this ambiguity. For example, the specification teaches that a heteroduplex, such as one with a damaged base, is treated with repair enzymes (e.g., glycosylase and AP endonuclease), which remove the base and some surrounding sequences on the strand comprising the damaged base thus producing a gap that is subsequently filled in by DNA polymerase I and DNA ligase. (e.g., Figures 1-3). The illustrations are not inconsistent with a strand always being annealed to another strand thus rendering the limitation "exposing" to repair enzymes superfluous and unclear. The claim must be amended to better clarify what is occurring as a result of exposing heteroduplex(es) to repair systems (enzymes) and what structure actually results from said exposure.

Claims 11-13 recite that particular "complex[es]" are individual enzymes. It is unclear how a single enzyme can concomitantly be a "complex" which by definition means additional components are necessary.

It would be remedial to replace "complex" with "enzyme" in base claim 10 and dependent claims 11-13. Alternatively, amending the claims to recite, "wherein said mismatch repair complex [base excision repair complex or nucleotide excision repair complex]

comprises..." would be remedial. Regarding, "combinations" it would be remedial to insert "of enzymes" between the terms "combination" and "thereof" to cover the scope sought.

Claim 14 recites the limitation "said parent polynucleotide", which lacks sufficient antecedent support.

Claims 22-23 recite the limitation "initial parent polynucleotide", which lacks sufficient antecedent support.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

2. **Claims 1-13, 15-18 and 20-27 are rejected under 35 U.S.C. 102(e) as being anticipated by Arnold et al. (US 6,537,746; see entire document; hereinafter the '746 patent).**

As noted above, independent claim 1 is vague and indefinite thus the claims' metes and bounds are indeterminable. However, in the interest of advancing prosecution, the claim is interpreted in light of the full disclosure, notwithstanding any ambiguities discussed above.

As such, claim 1 is directed to a method of preparing polynucleotide fragments wherein said method is defined by two positive action steps: (1) exposing heteroduplex polynucleotide(s)

to a "polynucleotide repair system"; and (2) denaturing said heteroduplex to obtain any single stranded fragment(s). Regarding the limitation "denaturing", since the step results in "said fragment", and "said fragment" is an "annealed fragment", the step is interpreted to mean there is denaturing followed by hybridization, otherwise "said fragment" cannot be an "annealed fragment". Further, without any temporal limitation, the heteroduplex is fragmented. (e.g., claims 2-5).

In addition, the fragment of claim 15 is limited to a range of about 15 to about X residues, wherein X is one residue less than the total number of residues in the longest polynucleotide in the reaction mixture. Given that the claim recites "**about** X" the range encompasses any fragment greater than about 15 nucleotides and less than the total number of residues in the reaction mixture.

The limitation "multiple cutting sites", relative to a restriction enzyme, literally reads on an enzyme for which multiple sites of a single particular recognition sequences are present. As such, the limitation is of little moment, because a restriction enzyme will cut recognition sequences, irrespective of how many of said sequences are present on a given DNA molecule.

The limitation "lacks polymerase, ligase or both" is interpreted to mean that where a repair enzyme comprises the "repair system" and said enzyme is the repair enzyme utilized to manipulate a heteroduplex, the enzyme is not polymerase or ligase. The limitation is not particularly defined in the specification, nor is the limitation further discussed therein. In addition, the limitation "damaged base" is not specifically defined in the specification thus is interpreted as broadly as reasonable to include mutated nucleotides.

With respect to claims 25-27, the claims are directed to a reaction mixture comprising fragments of at least two homologous heteroduplex polynucleotides. As such, the claims are directed to compositions. Thus additional limitations directed to how the polynucleotides are obtained or manipulated are deemed of little moment in determining whether the instant claims are distinguished from prior art that disclose a solution comprising said polynucleotides. Put another way, any manipulations therein are of little moment with respect to patentability, because the claim is a product-by-process type claim. Therefore when a reference teaches a product that appears to be the same or an obvious variant of the product set forth in a product-by-process claim although produced by a different process, then said reference anticipates the claim. *See In re Marosi*, 710 F.2d 799, 218 USPQ 289 (Fed. Cir. 1983); *See* MPEP § 2113.

The '746 patent teaches methods for creating polynucleotide sequences involving exposing heteroduplex polynucleotides to DNA repair systems, ultimately in evolving (i.e., shuffling) a polynucleotide toward acquisition of a desired property. (e.g., Abstract; Fig. 1; col. 2, ll. 35-67). More particularly, the reference teaches multiple iterations for combining homo- and heteroduplexes, where the different strands comprise imperfect complementation. (e.g., col. 2, last ¶, bridging to col. 3, ll. 1-47; col. 6, ll. 40-47; claim 1). The heteroduplexes are exposed to repair system so as to convert the heteroduplexes to parental polynucleotide variants (i.e., fragments). (e.g., col. 2, ll. 40-45; claim 7). The heteroduplexes can be exposed to repair systems *in vitro* or *in vivo*. (e.g., col. 2, ll. 47-54; col. 7, ll. 5-10; claims 3, 24).

The repair systems taught include *dam* methylation enzyme and related enzymes. (e.g., col. 14, ll. 5-38; claims 10,11). Additional repair systems include those involving the uracil

DNA glycosylase enzyme. (e.g., col. 23, ll. 29-35; claim 12). Further, the repair system involved can include DNA ligase. (e.g., col. 23, ll. 18-38; claim 13).

In addition, heteroduplexes are denatured into single-stranded molecules that are subsequently re-annealed. (e.g., col. 2, ll. 60-67; col. 3, ll. 20-30; col. 8, l. 65; claims 1, 9). Furthermore, the substrates for shuffling can be single stranded or double stranded DNA fragments. (e.g., col. 7, ll. 30-65; col. 8, ll. 38-49). The polynucleotide variants can comprise natural variants (i.e., native) or variants produced by mutagenic PCR. (e.g., col. 3, ll. 40-45; claims 6)

Heteroduplexes are digested with an endonuclease (i.e., fragmented with a restriction enzyme). (e.g., Figs. 3 and 14; col. 20, ll. 60-67; col. ; claims 2, 4, 21). Further, before exposing the heteroduplex polynucleotides to the repair enzymes (e.g., in a cell), point mutations resulting in mismatch residues are introduced into the heteroduplex polynucleotides. (e.g., Fig. 14; col. 21, ll. 52-67, bridging to col. 22, ll. 1-55; claim 16, 20, 22-23). Further, at least one strand of the heteroduplex can be methylated. (e.g., col. 21, last ¶; claim 17).

In addition, the reference teaches that dUTP can be added, for example in a PCR reaction, so as to introduce additional breaks into DNA upon repair by uracyl N-glycosylase in a host cell. (e.g., col. 23, ll. 29-35; claims 10, 18, 20). Furthermore, in any given reaction it is reasonable to conclude that a repair enzyme does not process every single mismatch on every single polynucleotide molecule. As a matter of fact, such a conclusion is specifically taught, where the reference explicitly teaches that recombination of different fragments (i.e., shuffling as mediated by a repair enzyme) becomes less efficient as a function of distance between any two mismatch sites. (e.g., col. 23, ll. 54-67, bridging to col. 24).

In addition, the '746 patent teaches fragments can vary in length from *about* 50 to 10^6 bases. (e.g., col. 8, ll. 37-39). One of skill will recognize that the term "about" is relatively open-ended (as is also utilized in claim 15). Furthermore, in the context of the claimed limitation "about 15....[to one less than full length]", the teaching of about 50 to various lengths up to 10^6 meets the claimed limitation because the upper limit set is the same and the lower limit set by the term "about" is of little moment in distinguishing the prior art from the claimed product.

Regarding "damaged" or mutagenized residues, the reference also teaches that polynucleotide sequences can be altered (i.e., damaged) by chemical mutagenesis, or achieved through irradiation with X-rays or ultraviolet light. (e.g., col. 7, last ¶, bridging to col. 8; claim 22-23). As to the claims directed to solution reactions, any which one of the solution reactions comprising the preceding combination of heteroduplex polynucleotides, including cytoplasm milieu, meet the claimed limitations of claims 25-26 (i.e., solution required to comprise heteroduplex polynucleotides that are damaged/mutagenized, and subjected to repair enzymes such as DNA glycosylase). In sum, the '746 patent anticipates the rejected claims.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ramin (Ray) Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached on Monday-Friday from 8:30-5:30. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 571-272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished

applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

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PATENT EXAMINER